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European Journal of Cancer 180 (2023) 158–179

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Controversies in the management of patients with soft tissue sarcoma: Recommendations of the Conference on State of Science in Sarcoma 2022

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https://doi.org/10.1016/j.ejca.2022.11.008

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Received 3 November 2022; accepted 4 November 2022
Available online 16 November 2022

KEYWORDS
Soft tissue sarcoma;
Diagnosis;
Imaging;
Peri-operative management;
Treatment of advanced disease;
Multimodal treatment;
Surveillance;
Policy;
Consensus

Abstract ***Background:*** Owing to the rarity and heterogeneity in biology and presentation, there are multiple areas in the diagnosis, treatment and follow-up of soft tissue sarcoma (STS), with no, low-level or conflicting evidence.
Methods: During the first Consensus Conference on the State of Science in Sarcoma (CSSS), we used a modified Delphi process to identify areas of controversy in the field of sarcoma, to name topics with limited evidence-based data in which a scientific and knowledge gap may remain and a consensus statement will help to guide patient management. We determined scientific questions which need to be addressed in the future in order to generate evidence and to inform physicians and caregivers in daily clinical practice in order to improve the outcomes of patients with sarcoma.
We conducted a vote on STS key questions and controversies prior to the CSSS meeting, which took place in May 2022.
Results: Sixty-two European sarcoma experts participated in the survey.
Sixteen strong consensus ($\geq$95%) items were identified by the experts, as well as 30 items with a $\geq$75% consensus on diagnostic and therapeutic questions. Ultimately, many controversy topics remained without consensus.
Conclusions: In this manuscript, we summarise the voting results and the discussion during the CSSS meeting. Future scientific questions, priorities for clinical trials, registries, quality assurance, and action by stakeholders are proposed. Platforms and partnerships can support innovative approaches to improve management and clinical research in STS.

1. Introduction

Soft tissue sarcomas (STSs) and connective tissue tumours of intermediate malignancy are rare, with an incidence of approximately 4–9/100,000/year in Europe. They can occur almost anywhere in the body, resulting in a wide variety of possible presentations. Most sarcomas arise in the extremities (ESTS), abdomen/retroperitoneum and trunk [1].

STS comprise approximately 150 sub-entities based on a combination of distinctive morphological, immunohistochemical and molecular features that often translate into a specific clinical behaviour [2]. Over the last few years, efforts have been made to base and refine the management of STS using this information. Many histotypes are exceedingly rare (in the range of 0.1 cases/100 000/year), to the extent that even specialized pathologists and clinicians may not encounter them more than once in their professional life. High-volume multidisciplinary sarcoma centres are therefore a prerequisite for optimal patient care.

The recent ESMO-EURACAN-GENTURIS (European Society for Medical Oncology; European Reference Network for Rare Adult Solid Cancers; European Reference Network for Genetic Tumour Risk Syndromes) guidelines provide comprehensive key recommendations on the management of soft tissue and visceral sarcomas from a multidisciplinary group of experts from different institutions, networks and European countries [3].

As expected, both these and other international guidelines focus on those areas of STS management, for which good-quality evidence is available. As a result, they do not cover controversial topics discussed among sarcoma experts in the absence of prospective data or in case of conflicting results from small retrospective or low-quality studies.

To address these issues, we organised the Conference on the State of Science in Sarcoma (CSSS) with international sarcoma experts. Our objective was to complement evidence-based guidelines, identify important areas for future clinical research and find ways to harmonise drug availability in Europe. We used the experience and

the methodology of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer and the Advanced Prostate Consensus Conference [4,5].

2. Methods

The panel included 62 sarcoma experts from 12 countries, covering different specialities involved in research and management of patients with STS (Appendix 1: CSSS panellists by country and speciality).

A sarcoma patient advocate was invited to attend and provide the patients' perspective during the CSSS conference.

Panel members were assigned to 12 working groups with different topics to formulate controversial issues in their areas of expertise (see Table 1).

During several rounds of virtual meetings, the 12 working groups developed and proposed various statements of controversy in their respective area of expertise. These statements were reviewed and prioritised by the CSSS board. Subsequently, 220 questions addressing controversial issues in STS diagnostics, peri-operative, local and palliative treatment, follow-up (FU), trial design and politics were presented to all panellists. Panellists were invited to vote on all topics, not just their area of specific expertise. In order to avoid bias, panellists lacking personal experience for a specific question were actively asked to answer with 'abstain'. Since some of the panellists did not answer all questions, the number of answers may vary in each voting category.

Panellists were instructed to assume that all statements generally applied to adult, non-frail patients, i.e. without limiting co-morbidities, or patients with other contraindications to the proposed treatments. Drug recommendations should be based on physician's choice rather than licence and/or availability. There were single selection and multiple-choice questions. A recommendation agreed upon by ≥75% panellists was defined as a 'consensus', while the term 'strong consensus' was used in case of ≥95% agreement among the panellists of all disciplines. Importantly, the process was also designed to allow the identification of areas without consensus, where additional data collection or future research was deemed necessary. CSSS also aimed to identify topics with limited evidence-based data, on which future high-quality studies were deemed unlikely, so that a consensus statement might help to guide patient management. Fig. 1 describes the CSSS process.

Following the debate at the May 2022 CSSS, a second survey was sent out to 31 panellists present and involved in the discussions during the meeting. For this second survey, 62 questions were selected, some of them re-phrased or specified. If the abstention rate was lower, the second vote was preferred (*). For close or identical results, the initial survey results are presented.

Table 1
Sarcoma working groups.

Pathology
Radiology
Surgery
Radiation oncology
Multidisciplinary group for peri-operative treatments
Medical oncology: subtype specific therapies
Multidisciplinary group for advanced, refractory and oligometastatic disease
Out of age
Gynaecology
Head and neck
Methodology, clinical trials
Politics

3. Management of patients with STS

CSSS covered the topics depicted in Fig. 2.

3.1. Diagnosis of STS

3.1.1. Clinical suspicion

There are still too many unplanned and inadequate excisions of soft tissue tumours outside of specialised sarcoma centres. Awareness in the medical community and among patients needs to be raised to a higher degree, and knowledge of how to manage a patient or better still, refer them to a sarcoma centre for any unexplained, enlarging, deep or superficial soft tissue mass ≥3 cm in diameter, as outlined in the ESMO guidelines, needs constantly to be reiterated. Guideline recommendations must address and also reach the patient's first point of contact, which is usually their general practitioner. Awareness campaigns are indispensable to reduce unplanned excisions that ultimately lead to morbidity, additional health care costs and deaths.

Patient representatives and organisations are needed to achieve this goal.

3.1.2. Pathology and imaging

3.1.2.1. Current state. The 5th Edition of the 2020 World Health Organisation (WHO) classification of tumours of soft tissue and bone is increasingly based on the molecular characteristics of sarcoma subtypes [2]. Understanding tumour molecular genetics improves diagnostic accuracy for tumours that have been difficult to classify based on morphology alone or that have overlapping morphologic features. A definition of a reference sarcoma pathologist is internationally lacking. Core needle biopsies can underestimate STS grading at diagnosis. Definition of a high-risk STS is not uniform. Superficial localisation is not well represented in risk stratification. The value of different histological response criteria to neo-adjuvant therapy is a matter of debate. There are ESMO recommendations on standard methods to detect neurotrophic tropomyosin-receptor kinase (NTRK)

Fig. 1. Process of CSSS. *CSSS, Conference on State of Science in Sarcoma.*

fusions in daily practice and clinical research; however, they are not consistently applied to STS tumours [6].

3.1.2.2. Controversy statements and CSSS voting. There was a 100% agreement that all mesenchymal tumours with unusual morphology, biological behaviour or with defined/known molecular aberration should be examined and validated by a reference sarcoma pathologist.

According to the panellists' majority opinion, a reference sarcoma pathologist should:

- be aware of new relevant diagnostic tools
- be a regular member of an interdisciplinary sarcoma board
- be specialized in sarcoma pathology and have worked for at least one year with a reference sarcoma pathologist
- regularly discuss cases with other reference pathologists
- evaluate at least 100 sarcoma cases per year
- implement quality assurance of sarcoma diagnoses
- be active in research and teaching
- cooperate with a laboratory of expertise
- perform next-generation sequencing (NGS)-based testing on a regular basis

There was also a strong consensus (97%) that a list of reference sarcoma pathologists should be made available on a regularly updated (inter-) national platform.

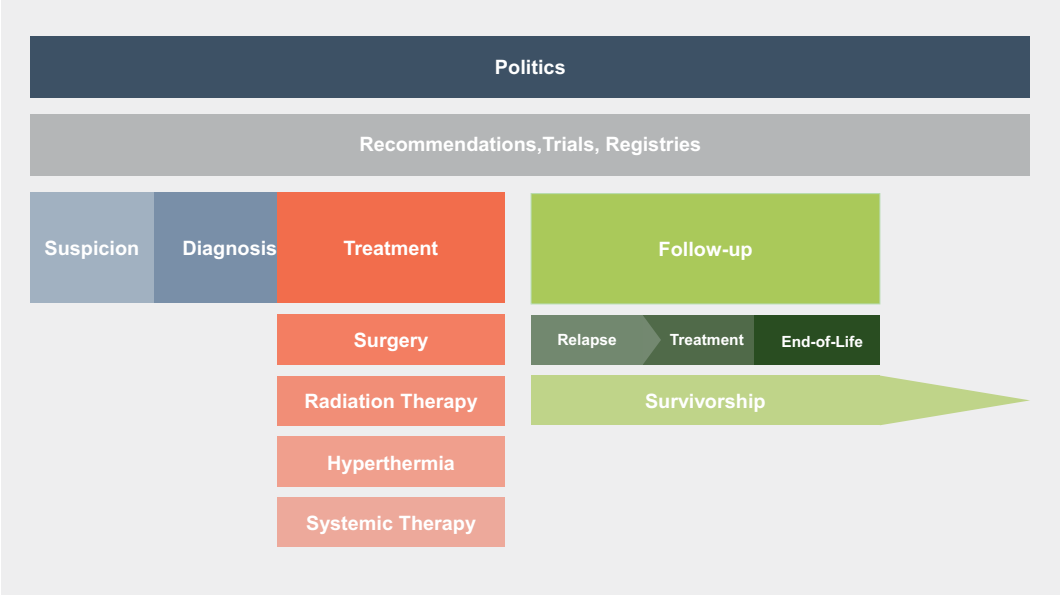


Fig. 2. Conceptual framework of CSSS. *CSSS, Conference on State of Science in Sarcoma.*

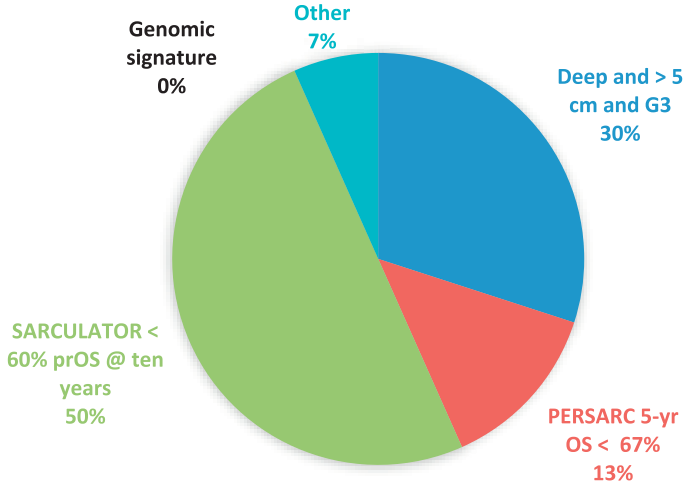
A prerequisite for the implementation of the peri-operative management of STS is a definition of STS risk categories, which must be agreed upon in the sarcoma community. While some sarcoma experts use molecular signatures, they usually rely on at least three parameters to define high-risk STS: a deep seated tumour, >5 cm in size and G3. Some panellists complement clinical risk assessment with the SARCULATOR/PERSARC tools [7,8] (Fig. 3∗).

Pathology grading is important in guiding decision making in the peri-operative setting. The widely used Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system is only validated and predictive for a subset of STS entities (undifferentiated sarcomas 'MFH' (now called undifferentiated pleomorphic sarcoma)), leiomyosarcomas (LMS), liposarcomas (LPS) and synovial sarcomas [9]. Other sarcoma subtypes are graded based on tumour entity or risk stratification schemes implemented in the WHO 2020 classification [2].

The fact that a diagnostic biopsy specimen may not be representative of the whole tumour, which is often heterogeneous in composition, further complicates accurate diagnosis and grading. Nevertheless, the initial biopsy will remain the only diagnostic specimen after neo-adjuvant treatment.

Histology from core needle biopsies has been shown to undergrade retroperitoneal LMS due to under-sampling of tumour necrosis as an example, and computed tomography (CT) was more sensitive in assessing necrosis in this situation [10]. Fusing advanced imaging and histology may help to enhance adequate grading and allow for new scoring tools both at diagnosis and after pre-operative treatment. CT or magnetic resonance imaging (MRI)-based radiomics may be used in the future to more accurately classify low- and high-grade sarcomas [11]. In case of discrepancies in grading between histology and radiology, 43% of the panel members, who do pre-operative external beam radiation therapy (EBRT), would postpone radiation therapy (RT) until after resection and work-up of the entire tumour, 57% of panel members would repeat the biopsy and postpone RT only if discrepancies remain.

Following neo-adjuvant chemotherapy (ChT) in STS, correlation between changes in tumour size on radiological images and patient prognosis is controversial. In addition, the value of different histological response criteria in evaluating the effect of neo-adjuvant treatment is a matter of debate. The answers to the CSSS question regarding the pathology response scoring system used in daily clinical practice were widely spread, ranging from 45% in favour of the Schaefer modification of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) scoring system, 3% using the Salzer-Kuntschik score and 7% mentioned miscellaneous criteria [12,13]. It remains unclear, which scoring system would currently be preferred since 45% of the panellists abstained from voting for this question, which may indicate that there is still no appropriate scoring system available. To complement pathology response criteria, panellists rely on multiparametric imaging changes (including positron emission tomography (PET)) and tumour volume



Panellists	31
Votes	30
Abstain	1

Fig. 3∗. Definition of high-risk STS by panellists. *G, grade; PERSARC, personalised sarcoma care.*

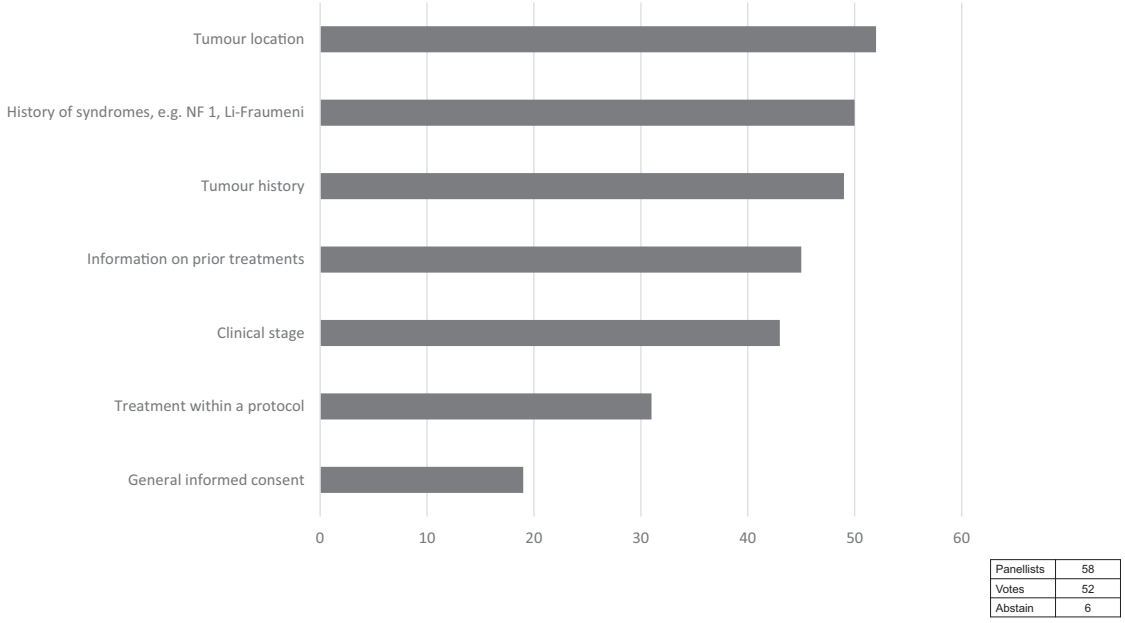


Fig. 4. Pathology request form (multiple answers possible). *NF, neurofibromatosis*.

change. There was an 82% consensus that advanced imaging (defined as additional functional exams beyond conventional morphological imaging, e.g. diffe on clinical outcome, (ii) the significance of tumour necrosis either as a sign of tumour aggressiveness or as a consequence of treatment, (iii) the value of viable tumour cells, (iv) treatment changes like fibrosis, hyalinisation and cell differentiation after neo-adjuvant therapy and (v) whether STS subtype-dependent assessment of response should be attempted.

Existing predictive and prognostic tools, such as PERSARC or SARCULATOR, should be further enriched by more parameters including additional subtypes, molecular data and type of treatment.

Updated and meaningful guidelines for the use of multigene panel sequencing should include STS subtypes.

Since there was absolutely no consensus by the CSSS experts on the best strategy to detect druggable *NTRK*-alterations, the ESMO guideline for malignancies in general could apply to STS for the time being. In

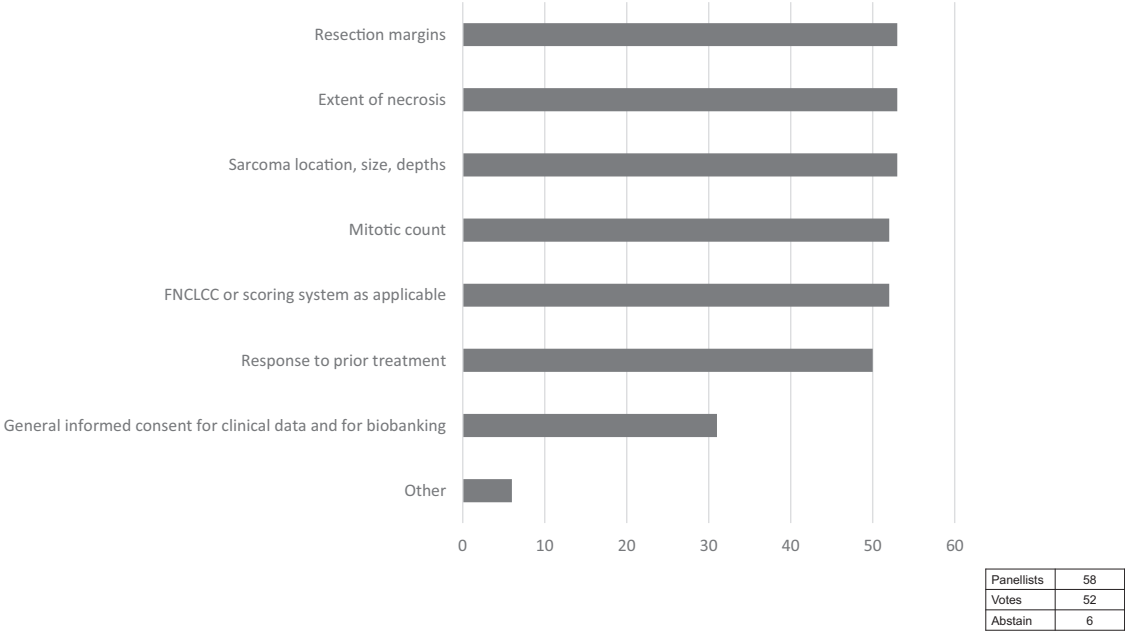


Fig. 5. Pathology report (multiple answers possible). *FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer*.

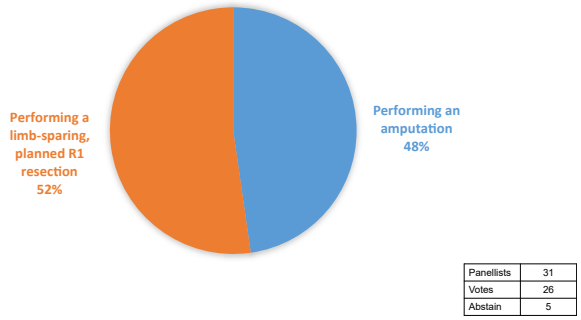


Fig. 6∗. In patients with localised ESTS, if wide surgical margins can only be achieved by ablative surgery after pre-operative multimodal treatment I usually recommend. *ESTS, extremity soft tissue sarcoma.*

sarcomas, where *NTRK* fusions are highly recurrent (e.g. infantile fibrosarcoma), flurescence in situ hybridization (FISH), reverse transcription–polymerase chain reaction (RT-PCR) or RNA-based sequencing panels can be used up-front. Whereas in the scenario of testing an unselected population, where *NTRK1/2/3* fusions are uncommon, either front-line sequencing (preferentially RNA-sequencing) or screening by immunohistochemistry followed by sequencing of positive cases should be pursued [6].

3.2. Treatment of STS

3.2.1. Local treatments

3.2.1.1. Surgery

3.2.1.1.1. Current state. The ESMO guidelines state clearly that surgery is the standard treatment for all patients with an adult-type, localised STS. It must be carried out by a surgeon specifically trained in the management of STS, and with the expertise of standard surgical procedures: this is an en-bloc wide excision with R0 margins. Nevertheless, unplanned sarcoma resections (also called 'whoops' resections) range internationally from below 20% to up to 40% [14,15].

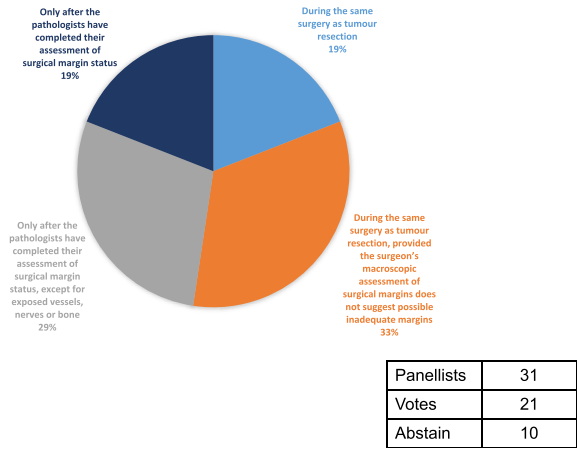


Fig. 7∗. In patients needing plastic reconstructive surgery following the resection of STS, I usually recommend reconstructive surgery to be performed.

In addition, a wide excision of a sarcoma is not defined uniformly among surgeons and depends largely on histotype. Prediction of a R0 or R1 resection is not possible for certain histologies (e.g. myxofibrosarcoma). In general, critical margins cannot be compensated by multimodal treatment.

For retroperitoneal sarcomas (RPS) the situation is further complicated. The Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPS-WG), a collaborative group for surgical oncologists and sarcoma professionals, is in the process of studying and recommending procedures for the management of RPS [16].

According to the TARPS-WG, R0 and R1 resections in RPS cannot precisely be distinguished or predicted. Therefore, it is more plausible to distinguish between a R0/R1 and a R2 situation.

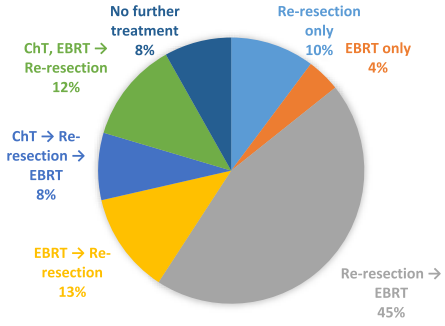
Salvage procedures after an unplanned sarcoma resection are managed inconsistently. There are retrospective data to support re-resection in case of macroscopically positive margins. However, in case of no residual disease on imaging, re-excision may be postponed [17].

An intermediate state between localised and metastatic disease is described as oligometastatic disease (OMD). An appropriate definition of OMD for STS is important because long-term control can be achieved for OMD. However, different forms of OMD most probably have different outcomes irrespective of treatment. There is a comprehensive characterisation of OMD for cancer in general, agreed by the EORTC and the European Society for Radiotherapy and Oncology [18]. OMD, described as a small number of growing or newly diagnosed metastases on imaging, is further characterised by a dynamic algorithm asking five consecutive questions:

1. Does the patient have a history of polymetastatic disease before the current diagnosis of OMD?
2. Does the patient have a history of OMD before the current diagnosis of OMD?
3. Has OMD been first diagnosed more than 6 months after the primary cancer diagnosis?
4. Is the patient under active systemic therapy at the time of OMD?
5. Are any oligometastatic lesions progressive on current imaging?

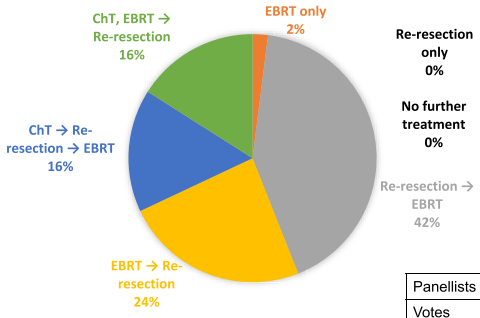
Importantly, the authors neither make a statement on the management of the primary tumour nor size or location of the metastatic lesions are mentioned. Questions remain also regarding the most appropriate imaging modality for OMD.

3.2.1.1.2. Controversy statements and CSSS voting. In patients with localised high-risk ESTS, if wide surgical margins can only be achieved by ablative surgery after pre-operative multimodal therapies, 46% of the



Panellists	59
Votes	49
Abstain	10

Fig. 8a. My recommendation in cases of an unplanned/inadequate resection *without* macroscopic tumour left, my option in high-risk ESTS and trunk wall sarcoma. *EBRT, external beam radiation therapy; ChT, chemotherapy*.



Panellists	59
Votes	50
Abstain	9

Fig. 8b. My recommendation in cases of an unplanned/inadequate resection *with* macroscopic tumour left, my option in high-risk ESTS and trunk wall sarcoma. *EBRT, external beam radiation therapy; ChT, chemotherapy*.

panellists usually recommend an amputation, whereas 54% offer a limb sparing planned R1 resection (Fig. 6*).

Sarcoma surgeons at CSSS consider a planned focal R1 resection to be comparable in outcome to the removal of all critical structures (e.g. vessels) as part of a multimodality approach, owing to the poor biology of the tumour in question [19].

No consensus was reached on whether plastic surgery should be performed directly after tumour resection or after pathologic work-up. Twenty-nine percent voted for plastic surgery only after the pathologist completed the assessment of margins, 33% recommend plastic surgery directly after tumour resection as long as the surgeon is certain about adequate margins, another 19% voted for plastic surgery always during the same procedure as tumour resection, 29% agreed with pathological work-up first, except for cases of exposed vessels, nerves or bone (Fig. 7*).

The preferred sequence of multimodal management of an unplanned R1 or R2 resection for high-risk ESTS or trunk wall sarcomas *without* macroscopic tumour remaining is depicted in Fig. 8a, in cases *with* macroscopic tumour left in Fig. 8b. Multimodality treatment comprising resection and RT is undisputed, 32% voted for additional ChT in case of macroscopic tumour remaining. There was no consensus on the sequence of therapies.

As previously mentioned, according to the TARPS-WG, R0 and R1 resections in RPS cannot accurately be distinguished or predicted. Therefore, it makes sense to distinguish between R0/R1 and an R2 situation. When asked about their recommendation in case of an R1 resection in RPS, 61% of panellists decided for no further treatment, which corresponds to the German S3 guideline [20].

In case of an *unplanned* RPS resection without macroscopic tumour remaining, >75% of the panellists opted for no further treatment (Fig. 9a*). Whereas, in cases where residual tumour was left, all panellists would re-resect with or without additional therapy such as RT or ChT (Fig. 9b*).

In case of a *marginally resectable* RPS dedifferentiated LPS (DDLPS), 60% of the panellists would treat with pre-operative ChT to render the sarcoma resectable, the number was even higher (67%) for G3 LMS.

While the EORTC-1809-STBSG (STRASS II) trial is recruiting patients to assess the role of neo-adjuvant ChT in certain RPS subtypes, the current management of RPS was discussed at CSSS [21].

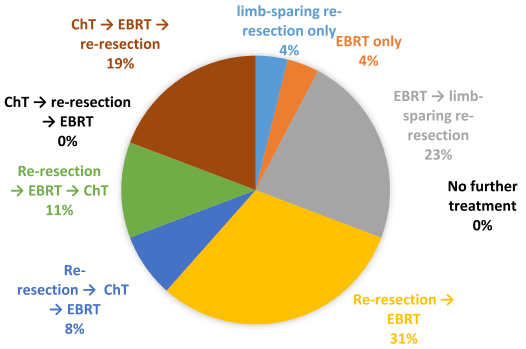
While 53% of the panellists voted for surgery only in localised *resectable* high-grade retroperitoneal DDLPS, 36% would apply ChT in a multimodal neo-adjuvant setting. Whereas in *resectable* high-grade retroperitoneal LMS, 54% of the panellists use neo-adjuvant ChT given the high distant metastases rate.

There was an 85% consensus not to combine local hyperthermia in case RT ± ChT was planned for high-risk resectable RPS. This may reflect the limited availability of hyperthermia in centres, rather than the existing scientific data. Therefore, the low approval rate should be interpreted with caution.

Seventy-one percent of panellists believe that the interpretation of the STRASS phase III trial results on pre-operative RT in RPS will change with longer FU and availability of the registry data (STREXIT, which has now been published) [22].

In case of an unifocal local recurrence without prior EBRT and without sarcomatosis of a retroperitoneal well-differentiated or low-grade DDLPS, pre-operative EBRT followed by re-resection 'in the majority of cases' was advocated by 68% of the panellist, by 27% of the panellists only 'in a minority of patients', and never by 5% of the panellists, 29% of panellists abstained for this question. Hence, more intense treatment is proposed in case of relapse and not as an initial approach for the tumours in question.

As there is no definition available for OMD in STS, panellists were asked to vote on criteria and could select multiple.



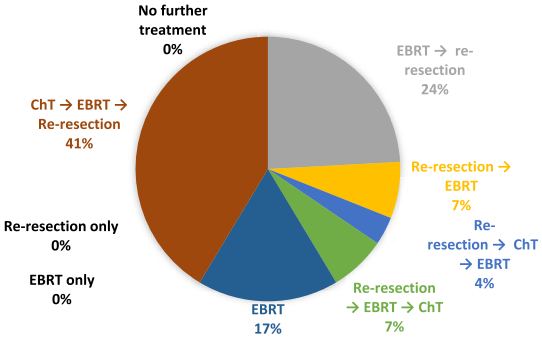
Panellists	31
Votes	26
Abstain	5

Fig. 9a∗. My recommendation in case of an unplanned resection (Whoops) *without* macroscopic tumour left in high-grade RPS. *EBRT, external beam radiation therapy, ChT, chemotherapy*.

Here, we show the ranking of the OMD criteria:

- number of metastatic lesions
- number of affected organs
- growth dynamic of metastatic lesions over time
- interval from primary tumour diagnosis
- patient under active treatment
- previous history of metastatic disease

We explored treatment strategies with curative intent for patients with STS and *synchronous* OMD to the lungs, i.e. systemic therapy and local modalities: 48% of the panellists would apply combined treatment 'in the majority of cases', 30% 'depending on the growth of metastatic lesions over time' and 22% 'in a minority of patients'. There was a consensus to re-scan after three months in patients with STS and *synchronous* OMD to the lungs and prior to local therapies to the metastases in order to rule out the appearance of new lesions.



Panellists	31
Votes	29
Abstain	2

Fig. 9b∗. My recommendation in case of an unplanned resection (Whoops) *with* macroscopic tumour left in high-grade RPS. *EBRT, external beam radiation therapy; ChT, chemotherapy*.

In cases with *synchronous* OMD to the lungs, amenable to surgery only by a lobectomy, 73% of the panellists preferred other local techniques (e.g. stereotactic RT or interventional radiological ablative techniques). However, for *metachronous* OMD to the lungs, amenable to surgery only by a lobectomy, there was a consensus (80% of the votes) for other local techniques instead of surgery.

In patients with *metachronous* OMD, 75% of the panellists recommend both systemic and loco-regional treatments. When asked whether patients with STS and *metachronous* pulmonary OMD should be treated by local modalities with curative intent, the following responses and limitations were given (Fig. 10).

Eighty-nine percent of panellists perform local therapies for stable or slow growing oligometastatic progressive disease.

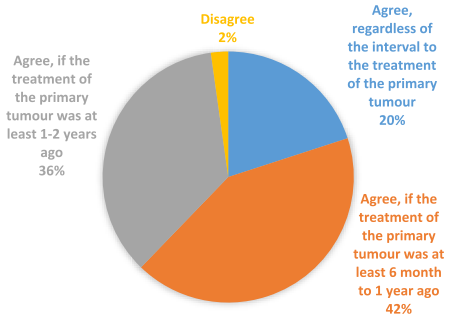
3.2.1.1.3. Areas identified for research and requests to policy. Health care systems, insurance companies, policymakers and stakeholders are encouraged not to reimburse sarcoma surgery outside of referral centres in order to ensure high-quality surgical interventions and to reduce the unacceptably high number of unplanned/inadequate sarcoma resections. Surgical societies and patient advocates should raise awareness of the problem. The Sarcoma Patients Advocacy Global Network (SPAGN) is an excellent network in this regard. Guidelines for the reimbursement of certain types of surgery are already in place in some countries (e.g. UK). The policy to refer patients with sarcoma exclusively to highly specialized centres should be implemented internationally.

Fifty-seven percent of CSSS panellists believe that the learning curve of an ESTS surgeon plateaus after 100 planned ESTS resections, while another 27% vote for at least 50 resections: taken together, a consensus was reached on at least 50 ESTS resections per sarcoma surgeon, which could provide guidance for health policymakers. The same question regarding RPS yielded similar results with 54% voting for 100 resections and an additional 30% voting for 50 RPS resections to plateau. No clear consensus was reached on the yearly number of STS resections to maintain surgical expertise: numbers ranged from 10 to 20 (32%), 30 to 40 (21%) and 40–50 (42%), respectively. It is noteworthy that more panellists voted for a higher caseload.

Outcome data from patients with ablative surgery versus limb sparing planned R1 resection should be collected in international registries since randomised control trials (RCTs) will not be feasible for this question.

There was a strong consensus (96%) that the surgeon's pre- and intra-operative prediction of an R0 resection should be documented and compared to the post-operative pathological findings (Fig. 11).

This form of quality control should be implemented in routine clinical practice.



Panellists	57
Votes	45
Abstain	12

Fig. 10. In patients with STS and metachronous oligometastatic disease to the lungs only, I treat with local modalities in curative-intent (e.g. metastasectomy, SBRT or radiological ablative techniques). *SBRT, stereotactic beam radiation therapy; STS, soft tissue sarcoma.*

A strong consensus could be achieved that STS principles and standard operating procedures of head and neck, dermatologic and gynaecologic surgeons should be in concordance with those of a reference sarcoma centre and discussed in a sarcoma multidisciplinary tumour board (MDT) prior to surgery. Panellists are aware that wide surgical margins can be difficult to achieve in regions such as head and neck, necessitating complementary local modalities such as RT.

RPS management should follow updated TARPS-WG recommendations and study results to find a safe balance between the extent of resection, multimodal approaches and complications thereof and ultimately outcome.

An attempt should be made to find a uniformly accepted definition of OMD in STS, and in a second step to work on an algorithm on how to proceed therapeutically. Registries such as OligoCare, an ESTRO-EORTC pragmatic observational basket study (EORTC 1822-RP) should include STS patients to solve the question whether repetitive local treatments have an impact on outcome in STS.

3.2.1.2. RT

3.2.1.2.1. Current state. The extent of resection after pre-operative RT and/or pre-operative ChT is not uniformly handled by the panellists.

The role of curative (aggressive) surgery in case of tumour progression during pre-operative therapies is not well established.

Pre- versus post-operative RT yields similar additive outcome results in high-risk ESTS or trunk wall sarcoma; however, side-effects, doses and radiation volume are different and there are no robust data on equal effects for RPS.

Optimal fractionations for STS have not yet been fully explored based on radiobiological criteria.

Concomitant RT and ChT have not been systematically studied in STS [23].

Re-irradiation and the relevance of the interval from primary treatment to re-irradiation to a radiation-associated angiosarcoma are discussed differently among radiation oncologists [24].

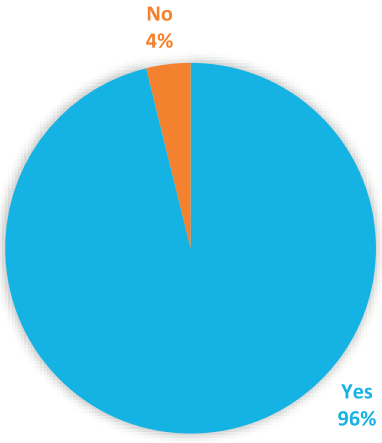
3.2.1.2.2. Controversy statements and CSSS voting. There was almost consensus (73%) to use RT pre-operatively and not post-operatively for resectable high-risk ESTS or trunk wall sarcoma. Panellists attending the CSSS meeting in May 2022 discussed situations where pre-operative RT might be difficult, e.g. in cases in need of vascular reconstruction, rapidly progressing primary sarcomas and discordance in grading of biopsy and imaging or in regions such as head and neck.

Sixty percent of the panellists think that there is weak evidence for the optimal time interval between pre-operative RT and subsequent surgery; they would consider a prospective study or registry for this question.

Following RT for localised STS, 55% of panellists plan the surgical resection on the residual tumour extension; the majority make an exception for STS initially infiltrating bone structures or STS with a known infiltrative biology, such as myxofibrosarcoma. Forty-five percent prefer to plan surgery on the initial tumour extension; the majority make an exception if this would result in mutilating surgery or functional disability. Similar results were obtained for the same question regarding neo-adjuvant ChT.

In case of local tumour progression during pre-operative treatment for localised STS, only 15% of panellists think quality of life (QoL) and functional consideration should be more important than aggressive surgical treatment with the aim of achieving wide surgical margins.

There is a strong consensus (98%) that tumours should be reimaged after pre-operative RT.



Panellists	59
Votes	52
Abstain	7

Fig. 11. I believe that the surgeon's prediction of a R0 resection should be documented during surgery and compared to the post-operative pathological findings (i.e. quality control).

There was almost a consensus (73% votes) that there should not be an additional boost in case of pre-operative EBRT and subsequent marginal resection.

In radiation-associated angiosarcoma, a third of panellists do re-irradiate the angiosarcoma, 27% of panellists use re-irradiation combined with hyperthermia whereas 37% of panellists did not use any further RT. Forty-five percent of those who did apply re-irradiation thought that the interval to the first RT was irrelevant.

3.2.1.2.3. Areas identified for research. Short course, hypofractionated pre-operative RT in high-risk resectable ESTS or trunk wall sarcoma should be further investigated since it may offer advantages over conventional fractionated RT. If post-operative wound healing and local control are not inferior to conventional fractionation, there will probably be a beneficial impact on costs, resources and QoL.

Special attention must be paid to the potentially different radiosensitivity of STS subtypes.

Concomitant RT with ChT or targeted therapy needs to be further studied to define its potential role on outcome.

More data on the role of RT in RPS have to be collected to define its impact for low- and high-risk sarcoma on long-term outcome.

3.2.1.3. Hyperthermia

3.2.1.3.1. Current state. There are data on synergism of regional hyperthermia and RT or ChT.

In high-risk STS, the addition of regional hyperthermia to peri-operative ChT resulted in increased overall survival (OS), as well as local progression-free survival in a phase III trial [25,26]. Yet, hyperthermia has not been widely adopted in sarcoma centres. This may be due to the necessary investment in technical equipment. In addition, the ChT regimen chosen by the investigators is not considered standard, and the data have not yet been reproduced and thus confirmed.

3.2.1.3.2. Controversy statements and CSSS voting. Only 12% of panellists combine peri-operative treatment in high-risk ESTS with hyperthermia in the majority of their patients, 25% in the minority of patients and 63% never.

Among panellists, who might consider hyperthermia, but have no equipment available at the institution, 27% recommend hyperthermia in the majority of patients, 38% in the minority of patients and would refer the patient. Very few panellists incorporate hyperthermia in the peri-operative management of high-risk retroperitoneal LMS or DDLPS.

3.2.1.3.3. Areas identified for research. Seventy-one percent of panellists agree on the statement that a confirmatory study is needed to establish the role of peri-operative ChT and/or RT with hyperthermia in STS, including RPS.

3.2.2. Systemic treatment

3.2.2.1. Peri-operative systemic treatment

3.2.2.1.1. Current state. There is only indirect evidence that peri-operative systemic therapy might be beneficial in high-risk resectable STS. In the most recent studies, a therapy-free control arm is lacking and subtypes are under-represented.

In the Italian, Spanish, French, and Polish Sarcoma Groups study of pre-operative ChT, the histotype-tailored arms lacking an anthracycline were associated with inferior survival compared with a combination of ifosfamide plus epirubicin, except in the case of myxoid LPS, where trabectedin resulted in equivalent outcomes [27].

3.2.2.1.2. Controversy statements and CSSS voting. Sixty-eight percent of the panellists believe that there is sufficient evidence to use pre-operative ChT in high-risk, resectable, localised ESTS or trunk wall sarcoma. The opinion expressed among the panellists was that sufficient evidence does not necessarily mean an optimal RCT, but enough studies all pointing in the same direction. In daily clinical practice, 49% do in fact use peri-operative ChT in the majority, while another 43% use it in the minority of their patients. For some panellists, a high-risk definition, as discussed before, is insufficient to indicate pre-operative ChT. They use additional factors, e.g. subtype and chemosensitivity. In case, panellists use ChT, 83% give it pre-operatively (consensus) and 12% post-operatively. Sixty-nine percent use an anthracycline/ifosfamide (A/I) combination, whereas 27% prefer histotype-specific regimens, e.g. anthracycline/DTIC for LMS or trabectedin for myxoid LPS.

Sixty-five percent treat with 3 neo-adjuvant cycles and 34% prefer to treat until best response or toxicity.

Still 59% of the panellists opted for a further clinical trial to compare peri-operative systemic treatment versus no such treatment/placebo in high-risk ESTS or trunk wall sarcoma. There was a broad distribution and no consensus on preferred peri-operative regimens for such a trial: 29% of the panellists voted for A/I for all high-risk STS, 26% for a histotype-specific regimen for all high-risk STS, 29% for A/I for specific STS subtypes and 13% for a histotype-specific regimen for specific STS subtypes. Fifty-six percent of panellists would choose OS as an appropriate endpoint for such a trial and 44% would prefer disease-free survival. Panellist were well aware that such an international trial would be difficult to conduct due to country bias, physician and patient reluctance to randomise and the rarity of subtypes.

Preferred sequences of multimodal therapies in daily clinical practice for high-risk, resectable ESTS or trunk wall sarcomas are depicted in Fig. 12*.

The following statements concern rare STS subtypes:

There was no consensus concerning the treatment of extraskeletal mesenchymal chondrosarcoma in the curative setting. While 35% of the panellist would use a Ewing protocol, 30% voted for A/I combination, 27% would not offer any ChT and 8% would use other unspecified regimens. On the other hand, there was a consensus to treat both BCOR (79%) and CIC-DUX (83%) round cell sarcoma according to Ewing sarcoma regimens.

In cases with localised high-risk extraskeletal osteosarcoma there was no consensus on treatment: half of the panellists voted for systemic treatment as for high-grade osteosarcoma, the other half would use systemic treatment as for STS.

Eighty-four percent of panellists agreed to treat paediatric-type rhabdomyosarcoma (RMS) up to the age of 60 and if fit, with paediatric regimens.

Seventy-two percent of panellists consider STS subtype agnostic clinical trials no longer appropriate for phase I/II and 76% think the same for phase III trials (Fig. 13).

A consensus (77%) was reached for the statement that adolescent and young adult (AYA) patients should be treated in centres equipped with dedicated paediatric and adult medical oncology teams.

A sarcoma medical oncologist should manage at least 30 patients per year, according to 58% of panellists or 20 patients according to 38% panellists.

Other criteria for medical oncologists included:

- participation in a weekly sarcoma MDT
- participation in at least one international sarcoma conference per year
- enrolment of patients in clinical trials
- participation in international networks
- experience in application of toxic drug combinations (e.g. high-dose methotrexate, platinum compounds)

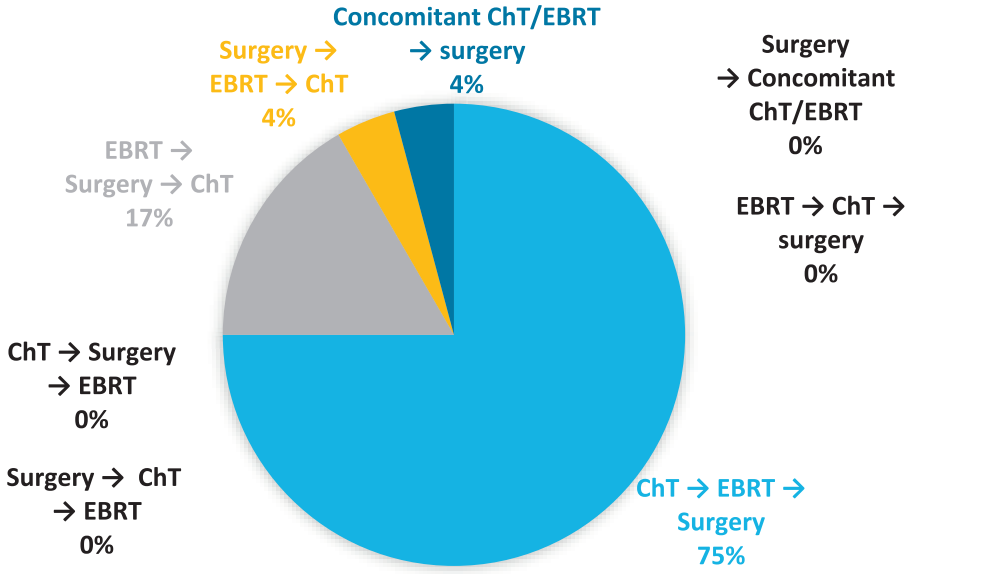
3.2.2.1.3. Areas identified for research. The role of peri-operative systemic therapy should be further studied, e.g. in registries or prospective databases and be compared by propensity score matching to circumvent the problems of enrolling patients in RCTs. Another alternative approach would be a RCT with a registry part for patients and physicians reluctant about the randomisation [28]. At the CSSS meeting, emphasis was placed on not stopping data collection too early to avoid missing long-term effects on patient outcome.

Integrated radiomic, metabolic and molecular data to investigate response to neo-adjuvant treatment are indispensable to achieve progress in this area.

Rare STS subtypes and their treatment need to be followed in international registries; outcome data should then be integrated in updated STS guidelines. Funding has to be made available by ministries of health, the European Union (EU) and other international funding organisations.

According to 94% of panellists, participation in national/international registries for ultra-rare sarcomas should be required for a certified sarcoma centre.

Quality control criteria for medical oncologists should be implemented, including interactions among medical oncologists that seem more important than patient numbers.



Panellists	30
Votes	24
Abstain	6

Fig. 12*. My preferred sequence in high-risk resectable ESTS and trunk wall sarcoma is. *EBRT, external beam radiation therapy; ChT, chemotherapy*.

National MDTs for ultra-rare sarcomas, including remote participation, would be simple and cost-effective quality improvement methods that are already in place in certain countries (e.g. the Interdisciplinary Ewing Sarcoma Board, Essen, Germany).

3.2.2.2. Systemic treatment in advanced STS

3.2.2.2.1. Current state. Palliative treatment has various goals: symptom control, improving or at least not affecting health-related QoL, prolonging life, inducing a remission or stabilising the disease. The duration of such a treatment varies greatly and depends mainly on the symptoms and wishes of the individual patient and the outcome parameters of the treatment in question.

'All-comer' studies for STS often failed and anthracycline-based first line therapies need to be challenged for various STS subtypes.

There are many individual sarcoma subtypes (e.g. alveolar soft part sarcoma, clear cell sarcoma, solitary fibrous tumours, extraskeletal myxoid chondrosarcoma) for which the most appropriate treatment is not conventional ChT but instead a specifically targeted treatment, based on the known molecular drivers of the disease, a multi-targeted receptor tyrosine kinase inhibitor (TKI), some form of immunotherapy or combinations thereof.

The problem for clinicians and, indeed, regulators is that some of these tumours are so rare that it is difficult, though not impossible, to conduct randomised clinical trials and provide the sort of high-level evidence usually demanded by bodies that advice on reimbursement. In some instances, the evidence comes from case series which together suggest that a particular treatment does result in disease stabilisation, tumour shrinkage, improvement in symptoms and possibly even prolongation of life.

Hence, many targeted therapies of rare subtypes e.g. EZH2 inhibitors in epithelioid sarcomas are not approved in Europe.

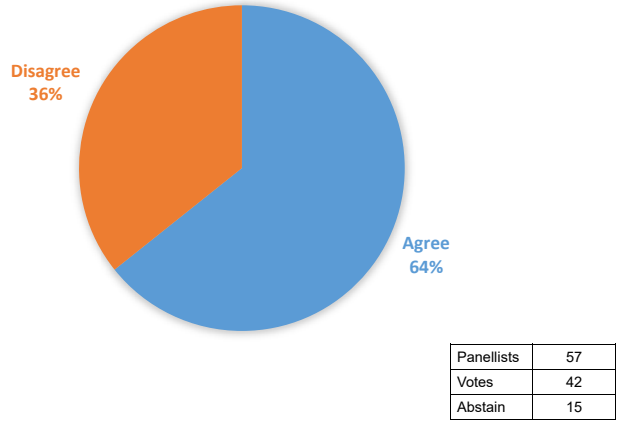


Fig. 13. STS subtype agnostic clinical trials are no longer appropriate in phase III.

Drug repurposing in general is not reimbursed outside of clinical trials. Pharmaceutical industry is usually not interested to conduct trials with drugs already on the market. Designs like the Drug Rediscovery Protocol (DRUP) are interesting to allocate patients on the basis of their molecular profile [29].

Key end-points for clinical trials in palliative treatment of advanced STS remain to be established.

One of the ESMO strategies, which has already begun and is future-oriented, is to convene meetings, bring together experts from several disciplines, to formulate recommendations and create consensus papers for various sarcoma subtypes, such as epithelioid haemangioendotheliomas [30] (Table 2).

3.2.2.2.2. Controversy statements and CSSS voting. There was a consensus on the main goal of palliative treatment in symptomatic patients: eighty-six percent of the panellists voted for symptom control and only 12% prefer prolongation of life as a main goal. Maintenance of QoL in asymptomatic patients was an important aim for 61% of the panellists, followed by prolongation of life for 31%.

In cases where NGS reveals a result with potential therapeutic consequences, 55% of panellists still give standard STS treatment first line (e.g. doxorubicin monotherapy), especially in chemo-sensitive tumours or due to restrictions. Twenty-three percent give NGS-guided treatment in first-line.

When asked whether to stop TKI treatment in patients with controlled disease, 49% of panellists do so in the event of unacceptable toxicity of the TKI, 31% at the patient's request. Only 10% do so after achieving confirmed stable disease in a patient with no symptoms of the tumour.

There was a strong consensus (100%) that in STS with slow/minimal growth rate randomised discontinuation trials should be performed: after a defined timepoint and stable disease, patients should be randomised to continue study drug or placebo.

Eighty-one percent of panellists consider single-arm trials appropriate for advanced/metastatic STS, especially in rare STS subtypes. In such a single arm trial, 72% voted for progression-free survival as an appropriate end-point, followed by objective response rate (12%) and disease control rate, and patient reported outcome measures (PROMs) (<10% each). The question arises, why only 10% of the panellists voted for PROM as this is an appropriate end-point in advanced disease. However, PROM are neither commonly used in daily clinical practice for STS (only by a third of the panellists) nor are specific PROM questions for STS patients well characterised.

3.2.2.2.3. Areas identified for research and requests to policy. Repurposing of drugs that are already approved for other diseases should be facilitated by health care authorities and regulators in order to treat STS.

Novel treatments for advanced as well as for newly diagnosed STS and approval thereof require multinational efforts and appropriate study designs.

Table 2
An up-to-date list of treatments for rare STS subtypes with evidence for regular use according to CSSS. The panellists therefore recommend to make these drugs available to patients and reimbursed internationally.

STS Subtype	Characteristics for treatment choice	Drug
Extraskeletal myxoid chondrosarcoma	*EWSR1-NR4A3* gene fusion	Pazopanib [42]
Solitary fibrous tumour	Typical, i.e. low aggressiveness	Antiangiogenic TKI [43,44]
Desmoid tumour		Sorafenib [45] Pazopanib [46]
Alveolar soft part sarcoma		Cediranib, or other TKI [47,48] Atezolizumab [49] Axitinib + pembrolizumab [50] Sunitinib + nivolumab [51]
Epithelioid haemangioendothelioma		TKI [30]
Inflammatory myofibroblastic tumour		ALK inhibitor [52]
Epithelioid sarcoma		Tazemetostat [31]
PEComa		Nab-Sirolimus [53] Everolimus [54]
Undifferentiated pleomorphic sarcoma		Checkpoint inhibitor [55]
Angiosarcoma	Radiation-associated	Checkpoint inhibitor [55]

The question of continuous or intermittent drug administration in the palliative setting and after disease stabilisation should be investigated in academic clinical studies.

CSSS consensus statements should inform decisions by health care organisers and regulators since efficacy and effectiveness of certain drugs does not equate to their availability.

For example, tazemetostat should be made available for use in epithelioid sarcomas, which was supported by 91% of the panellists [31], despite the fact that the phase II tazemetostat data did not meet the ESMO Magnitude of Clinical Benefit Score criteria (MCBS) [32].

A consensus (79%) could be reached that academic trials should investigate dosing of TKI in STS according to individual serum levels and not to follow the recommendations from registration trials only.

Patient relevant trial end-points of palliative STS treatment should be discussed with patient advocates and PROM needs to become a standard measure.

Algorithms with criteria for reimbursement of drugs in the palliative setting should be adopted from

Table 3
Statements with strong CSSS consensus (≥95%).

1. A list and network of reference sarcoma pathologists should be made available on a regularly updated (inter-) national platform
2. Mesenchymal tumours with unusual morphology, biological behaviour or with detectable molecular aberration should be examined/validated by a reference pathologist
3. In general, resection strategies in patients with STS should be based both on tumour characteristics and surgical morbidity/function preservation
4. I believe that the recommended surgical margin width and the optimal resection strategy should take into consideration what is technically feasible or necessary at different anatomical sites (e.g. head and neck, spine, extremities, retroperitoneum and skin)
5. The surgeon's prediction of a R0 resection should routinely be documented during surgery and compared to the post-operative pathological findings (quality control)
6. The STS principles and SOPs of head and neck, dermatologic and gynaecologic surgeons should be in concordance with those of a reference sarcoma centre and discussed within a MDT prior to surgery
7. After pre-operative EBRT, the tumour should be re-imaged
8. If pre-operative EBRT is applied for ESTS and trunk wall sarcoma, my standard RT regimen is (myxoid LPS excluded) 50 Gy equivalent regimen in 1.8–2 Gy once-daily fractions
9. To establish the need of treatment in EHE, I perform a confirmatory follow-up scan
10. For newly recognised molecular entities, all patient should be collected in international registries
11. National strategies for social/financial integration of AYA patients are required
12. National support groups with access to pain management experts, physical, occupational therapists, mental health workers and financial advice on paying for health care should be available within survivorship care for AYA patients
13. In future trials, a combined response score from pathology and radiology is required
14. STS trials in general should cover a broad age range in order to capture as many patients as possible with 'out of age' sarcoma
15. STS treatment should be assessed within basket/umbrella trials (e.g. new candidate drugs for patients with rare molecular alterations)
16. In STS with slow/minimal growth rate, randomised discontinuation trials should be performed (i.e. after a defined time-point and stable disease, patient should be randomised to continuous study drug or placebo)

CSSS, Conference on State of Science in Sarcoma; STS, soft tissue sarcoma; SOP, standard operation procedure; MDT, multidisciplinary tumour board; EBRT, external beam radiation therapy; ESTS, extremity soft tissue sarcoma; RT, radiation therapy; LPS, liposarcoma; Gy, Gray; EHE, epithelioid haemangioendothelioma; AYA, adolescents and young adults.

European guidelines and take the ESMO MCBS into account, which have been recently applied to several STS subtypes [33,34]. Pay for performance models coupled with data collection and Cancer Medicine Forum (a European Medicines Agency and EORTC cooperation) were discussed at the CSSS meeting [35].

Growth dynamic and bulk of the disease should be part of the inclusion criteria in order to avoid negative trials.

There was a strong consensus (96%) among panellists that STS trials in general should cover a broad age range in order to capture as many patients as possible with 'out of age' sarcomas. However, 37% of panellists think that STS trials in general should be performed separately in children and adults. Eighty-two percent of panellists think that adult-type sarcomas that occur in children/AYA should be discussed with an adult medical sarcoma oncologist at a sarcoma tumour board.

3.3. FU and survivorship

3.3.1. Current state

The ESMO guidelines state that there are only few published data to indicate the optimal routine FU policy of surgically treated patients' localised STS disease. They also mention that the use of MRI to detect local relapse in the extremities and superficial trunk and a CT to detect lung metastases would be likely to pick up recurrences earlier. However, impact of early detection

Table 4
Statements with CSSS consensus (≥75%).

1. In patients with suspected ESTS or trunk wall sarcoma, usually a core needle biopsy for histological diagnosis is recommended
2. The radiographic features of a STS provide important additional information and should be considered when estimating STS grade, especially if tumour grading is not conclusive on biopsy
3. Advanced imaging plays a role in the peri-operative response assessment as part of routine practice
4. The principles of pre-operative and post-operative EBRT for head and neck sarcomas follow the same recommendations as for ESTS
5. ChT in high-risk resectable localised ESTS or trunk wall sarcoma is preferentially used pre-operatively
6. In case, I decide to use peri-operative ChT in high-risk resectable localised ESTS and trunk wall sarcoma, I give all ChT pre-operatively
7. In case, I decide to use EBRT ± ChT in high-risk resectable RPS, I do not combine it with regional hyperthermia
8. CIC-DUX and BCOR round cell STS at this point in time should be treated peri-operatively according to ES protocols
9. In patients with metachronous oligometastatic disease, I usually recommend both systemic and loco-regional treatments
10. In cases with metachronous oligometastatic disease to the lungs only, amenable to surgery only by a lobectomy, I prefer other local techniques (e.g. stereotactic radiotherapy or interventional radiological ablative techniques)
11. I perform local therapies for stable or slow growing oligometastatic progression
12. I perform active surveillance for patients with indolent disease (e.g. EHE) in the palliative setting
13. Main aim of palliative treatment in a symptomatic patient is symptom control
14. Use of drugs as mentioned in Table 2
15. To establish the need of treatment in EMC, I usually perform a confirmatory follow-up scan at progression
16. I differentiate my treatment in metastatic or advanced SFT on pathology i.e. DD SFT or low-aggressive (typical) SFT
17. Pleomorphic and sclerosing/spindle cell RMS should be treated with an anthracycline-based ChT
18. Paediatric-type RMS in fit patients should be treated with paediatric regimens up to the age of 60y
19. Academic trials should investigate dosing of TKI according to individual serum levels and not only follow recommendations from registration trials
20. Data on clinical outcomes of patients with STS should be included in a pan-European registry
21. AYA patients should be treated in centres equipped with a dedicated paediatric and adult medical oncology team
22. Adult-type sarcomas occurring in children/AYA should be discussed with a medical oncologist for adult sarcomas and as part of a sarcoma MDT
23. QoL, socioeconomic (including insurance issues) and psychological aspects should be systematically and longitudinally assessed in daily clinical practice, as foreseen in international ongoing projects
24. A survivorship care plan should be made available to all STS patients
25. Transition from paediatric to adult care should be facilitated by an international validated survivorship care program
26. Local tumour control for high-risk ESTS or trunk sarcoma should be done with MRI
27. Frequency of FU-intervals and modalities for high-risk ESTS or trunk sarcoma
28. I advise post-operative follow-up to my patients with uSarcoma with imaging every 3–6 months
29. Participation in national/international registry platforms for rare sarcomas is required for a certified sarcoma centre
30. Surgery of STS outside of reference centres should not be reimbursed

CSSS, Conference on State of Science in Sarcoma; ESTS, extremity soft tissue sarcoma; ChT, chemotherapy; ES, Ewing sarcoma; EHE, epithelioid haemangioendothelioma; EMC, extraskeletal myxoid chondrosarcoma; SFT, solitary fibrous tumour; DD, dedifferentiated; RMS rhabdomyosarcoma; y, years; TKI, tyrosine kinase inhibitor; STS, soft tissue sarcoma; AYA, adolescents and young adults; MDT, multidisciplinary tumour board; QoL, quality of life; MRI, magnetic resonance imaging; FU, follow-up; uSarcoma, uterine sarcoma.

Table 5
Selection of statements without a CSSS consensus.

1.	Definition of high-risk STS
2.	Criteria of response assessments and most important assessment modalities for STS
3.	Time point for NGS in the palliative setting
4.	Extend of resection following pre-operative EBRT or ChT for localised STS
5.	In case of local tumour progression during pre-operative treatment of localised STS, whether aggressive surgical treatment aimed at achieving wide surgical margins is more important than considerations of QoL and functional status
6.	Recommendation for patients with localised ESTS, when wide surgical margins can only be achieved by ablative surgery after pre-operative multimodal treatment
7.	Time point of plastic reconstructive surgery following resection of STS
8.	Time point of peri-operative EBRT (pre- versus post-operative)
9.	Optimal time interval between pre-operative EBRT and subsequent surgery
10.	Preferred treatment sequence in high-risk resectable ESTS or trunk wall sarcoma
11.	Hyperthermia in combination with peri-operative EBRT ± ChT in high-risk resectable, localised ESTS, trunk wall sarcoma and RPS
12.	Recommendations following an unplanned R1/R2 excision (whoops resection) of a high-risk ESTS or trunk wall sarcoma with or without macroscopic tumour left
13.	Re-irradiation and interval of RT of a radiation-associated angiosarcoma
14.	Level of evidence to use pre-operative ChT in high-risk resectable, localised ESTS or trunk wall sarcoma
15.	Type and number of cycles of ChT used peri-operatively
16.	Whether a further clinical trial is needed to compare peri-operative systemic treatment versus no systemic treatment/placebo in high-risk resectable, localised ESTS or trunk wall sarcoma
17.	Design and primary end-point of a peri-operative trial for high-risk resectable ESTS or trunk wall sarcoma
18.	Peri-operative treatment of EMCS
19.	Systemic treatment of high-risk extraskeletal osteosarcoma
20.	Main aim of palliative treatment in a patient without symptoms
21.	Stopping criteria in a patient on ChT or TKI
22.	Tools to estimate prognosis in daily clinical practice
23.	Use of geriatric assessments
24.	Definition of AYA
25.	Who should manage survivorship and FU of patients with STS
26.	Standard FU modalities for high-risk ESTS or trunk sarcoma and surveillance of metastatic sites
27.	Primary trial end-point in advanced/metastatic STS

CSSS, Conference on State of Science in Sarcoma; STS, soft tissue sarcoma; NGS next generation sequencing, EBRT, external beam radiation therapy; ChT, chemotherapy; QoL, quality of life; ESTS, extremity soft tissue sarcoma; RPS, retroperitoneal sarcoma; RT, radiation therapy; EMCS, extraskeletal mesenchymal chondrosarcoma; TKI, tyrosin kinase inhibitor; FU, follow-up; AYA, adolescents and young adults.

is always a matter of debate and most probably depends on the biology of the disease.

3.3.2. Controversy statements and CSSS voting

There was consensus (76%) that standard FU procedures for high-risk STS or trunk wall sarcomas should include the local surveillance of the primary tumour with MRI, only 22% voted for physical examination alone. In addition, standard FU procedures for high-risk ESTS or trunk wall sarcoma should include:

- CT chest (37% votes)
- CT chest and abdomen (29% votes)
- Chest X Ray (26% votes)
- Whole body MRI (4% votes)
- PET CT (4% votes)
- No routine imaging (0% votes)

Survivorship FU for patients with STS should be managed by:

- Survivorship clinic (50% votes)
- Medical oncologist (33% votes)
- General practitioner (6% votes)

Others (11%) suggest FU should involve radiation-, surgical- or medical oncologists, in collaboration with a survivorship clinic.

FU and survivorship care for patients with STS should be individualised according to STS subtype, location, recurrence risk and treatment according to the majority of the panellists. Some panellist place hope in

future technologies, e.g. circulating tumour DNA during FU.

Others use prognostic tools like PERSARC or SARCULATOR to guide individualised FU. Most panellists voted for a 10 year or lifelong FU period. There was a consensus (82%) for local surveillance of the primary tumour site and metastatic sites 3-monthly for the first two years, then 6-monthly until year 5, then annually.

Ninety-four percent agree that a survivorship plan should be made available to all patients with STS, although the exact content of such a plan was not discussed.

3.3.3. Areas identified for research and requests to policy

There was a consensus (86%) that health-related QoL, socio-economic (including insurance) and mental issues of patients with STS should be recorded systematically and longitudinally in daily clinical practice according to international ongoing projects.

Ninety-six percent of panellists strongly support national strategies for social/financial integration of AYA STS patients. National support groups with access to pain management experts, physical and occupational therapists, mental health workers and financial advice on paying for health care should be available within survivorship care for AYA patients, according to 94% of panellists.

Internationally accepted survivorship plans should be handed to STS survivors to provide a structured FU, adapted to ongoing study results.

Ongoing projects to solve IT and legal aspects should be promoted internationally.

3.4. Resource implications and politics

A particular concern of the CSSS is that drugs are made available and can be used in clinical practice even if there are only small case series or studies demonstrating their effectiveness.

Many of the panel's recommendations have important resource implications that could limit their utilisation due to financial or drug reimbursement constraints.

Drug access protocol (DAP) is a programme in the Netherlands to combine earlier access to medicine with structured data collection [36]. The benefits of the DAP in providing conditional reimbursement of registered drugs and thereby creating access are evident. However, the effects of the protocol in the setting of compassionate use (typically free of charge) require further exploration.

Similar programmes covering compassionate use, evidence generation and reimbursement are already in effect in England (Early Access to Medicines Scheme) and France (L'Accès Précoce) [37,38]. The current set-up of access to compassionate use in Europe has led to a patchwork of national access pathways [39].

A referral system has been implemented by EURACAN [40]. According to EU law and under certain circumstances, patients have the right to seek medical treatment, such as consultation with a specialist, surgery or treatment for a specific condition, in other EU countries, provided that the intended treatment is not available in their country [41].

4. Conclusion, outlook and perspective

In the absence of evidence or in areas where there are conflicting data or interpretation thereof, weighted expert recommendations can be helpful for making decisions in daily clinical practice and to design future trials. This was the guiding principle, motivation and goal when we initiated CSSS. During the preparation and at the CSSS meeting, we discussed and voted on different management options for patients with STS with European sarcoma experts. In some areas, a consensus could be reached. For a variety of sarcoma management aspects, future research questions could be formulated, whereas for some topics, there will probably never be sufficient data or a consensus. All panellists were aware that expert opinion is not equivalent to high-level evidence and that current expert opinions may be disproven by future clinical research. We could identify several areas ready to be addressed scientifically. An important issue for every consensus conference remains open to what extent are expert consensus meetings able to contribute to the adoption of unproven or controversial procedures and how much will they be able to influence health regulators?

There was a unanimous agreement among the experts that national registries should be mandatory, they should implement data sharing with international registries, they should allow pseudonymised data transfer, they should provide regular analysis of the data collected to complement national/international guidelines. However, transfer and ownership of the data were an issue during the discussion. We call for administrative hurdles to be reduced in the future and for facilitated patient access to innovations. EURACAN sets an example by promoting data and knowledge sharing for rare cancers such as sarcomas and plans to use a federated learning approach, which enables to perform analysis across multiple decentralised data sources, without exchanging their data.

Notable areas of consensus or disagreements of the CSSS voting are summarised in Tables 3–5.

A second CSSS 2024 is planned to address unresolved issues and emerging topics.

Author contribution

Study concept and design: All authors.
Acquisition of data: All authors.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: None.
Obtaining funding for CSSS meeting: SH and CR.
Administrative, technical, or material support: None.
Supervision: SH and CR.
Other: None.

Conflict of interest statement

The authors declare following conflicts of interest:

CR: Consulting or Advisory Role (Payment to Institution): Bayer (Schweiz) AG, Bristol-Myers Squibb, Ipsen, MSD Oncology, Pfizer; Consulting or Advisory Role (Payment to me): Merck (Schweiz) AG; Travel Expenses (Payment to me): PharmaMar; Research Funding (Payment to Institution): Astellas Pharma AG.

DA: has received institutional research support from Implantcast GmbH and invited speaker fees from PharmaMar.WGK: served as advisor to Bristol Myers Squibb, unrelated.

JYB: grants or research support from AstraZeneca, Bayer, Bristol Myers Squibb, Deciphera, Glaxo SmithKline, Merck Sharp & Dohme, Novartis, PharmaMar, and Roche; has an advisory or board member role in Innate Pharma; and receives honorarium from Bayer, Deciphera, Novartis, and Roche.

ID: no COI.

PD: Honoraria for consultancy or advisory role: Ayala Pharmaceuticals, Deciphera.

RH: no COI.

JJ: has received travel expenses or honoraria for participation in advisory boards or invited speaker fees from PharmaMar, Pfizer and Belpharma.

LHL: Honoraria and compensation for advisory boards: Boehringer Ingelheim, Novartis, Lilly, Eisai, EL Medconsult, Roche; Travel and research grants: Dr. Sennewald Medizintechnik; Travel grants: PharmaMar; Stockownerships: Thermosome (co-founder)

CM: no COI.

ABM: Trustee Sarcoma UK, no other conflict of interest.

TB: reports personal fees from PharmaMar and Deciphera (lecture fee, advisory board)

ABM: Trustee Sarcoma UK, no other conflict of interest.

RLJ: Receipt of grants/research support: MSD, GSK.

Receipt of consultation fees: Adaptimmune, Astex, Athenex, Bayer, Boehringer Ingelheim, Blueprint, Clinigen, Eisai, Epizyme, Daichii, Deciphera, Immunedesign, Immunicum, Karma Oncology, Lilly, Merck, Mundipharma, Pharmamar, Springworks.

SynOx, Tracon, Up to Date.

IJ: No conflicts of interest.

PR: has received honoraria for participation in advisory boards for Bayer, Novartis, Roche, Deciphera, Mundibiopharma, PharmaMar, Blueprint Medicines, GSK, Boehringer Ingelheim and invited speaker fees from Clinigen, Deciphera, PharmaMar, Boehringer Ingelheim.

JS: Participation in advisory boards or invited speaker fees: PharmaMar, Bayer, Roche, Lilly, Amgen; Travel expenses: PharmaMar, Roche, Lilly, Amgen, Bristol Myers Squibb; Research funding: PharmaMar, Roche, Eisai.

WvdG: research grant funding from Eli Lilly, advisory board participation Springworks, Bayer, PTC Therapeutics – all to the institute.

WJvH: received institutional honoraria for participation in advisory board for Belpharma, invited speaker fees from Amgen andreports expert testimony for Sanofi and MSD and personal travel grant from Novartis and institutional research grant from BMS.

EW: has received honoraria for participation in advisory boards or invited speaker fees from Bayer, Roche, Deciphera, Boehringer Ingelheim, Bristol Myers Squibb, PharmaMar.

SH: no COI.

Acknowledgements and funding

The authors would like to acknowledge the input of the patient advocate Sander Botter and the organisational support by COR2ED.

There was no financial remuneration for the CSSS initiative and the CSSS process.

The IT support for the voting and the CSSS hybrid meeting were financially supported.

The authors would like to acknowledge support from Kantonsspital St. Gallen and the financial support of the CSSS meeting from Swiss Cancer Research and Thomas Cerny, Lotte und Adolf Hotz Stiftung, Bayer, Bristol-Myers Squibb, Deciphera, Ipsen Pharma, Novartis, PharmaMar, Roche.

Appendix 1. CSSS panellists by country and speciality

Andreou	Dimosthenis	Surgery	Germany
Barth	Thomas	Pathology	Germany
Bauer	Sebastian	Medical Oncology	Germany
Blay	Jean-Yves	Medical Oncology	France
Blum	Veronika	Medical Oncology	Switzerland
Bode	Beata	Pathology	Switzerland
Bonvalot	Sylvie	Surgery	France
Bovee	Judith	Pathology	The Netherlands
Braam	Petra	Radiation Oncology	The Netherlands
Brodowicz	Thomas	Medical Oncology	Austria
Dei Tos	Angelo	Pathology	Italy
Denschlag	Dominik	Gynaecology	Germany
Desar	Ingrid	Medical Oncology	The Netherlands
Digklia	Antonia	Medical Oncology	Switzerland
Dileo	Palma	Medical Oncology	UK
Dirksen	Uta	Paediatric Oncology	Germany
Douchy	Thomas	Surgery	Belgium
Duffaud	Florence	Medical Oncology	France
Eriksson	Mikael	Medical Oncology	Sweden
Fröhling	Stefan	Medical Oncology	Germany
Gelderblom	Hans	Medical Oncology	The Netherlands
Gronchi	Alessandro	Surgery	Italy
Haas	Rick	Radiation Oncology	The Netherlands
Hardes	Jendrik	Surgery	Germany
Hartmann	Wolfgang	Pathology	Germany
Hofer	Silvia	Medical Oncology	Switzerland
Hohenberger	Peter	Surgery	Germany
Hompes	Daphne	Surgery	Belgium
Huang	Paul	Pathology	UK
Italiano	Antoine	Medical Oncology	France
Jakob	Jens	Surgery	Germany
Jones	Robin	Medical Oncology	UK
Judson	Ian	Medical Oncology	UK
Köhler	Günter	Gynaecology	Germany
Kollàr	Attila	Medical Oncology	Switzerland
Krasniqi	Fatime	Medical Oncology	Switzerland
Krol	Stijn	Radiation Oncology	The Netherlands
Kunz	Wolfgang	Radiology	Germany
Le Grange	Franel	Radiation Oncology	UK
Le Pechoux	Cécile	Radiation Oncology	France
LeCesne	Alexandre	Medical Oncology	France
Leithner	Andreas	Surgery	Austria
Liegl-Atzwanger	Bernadette	Pathology	Austria
Lindner	Lars	Medical Oncology	Germany
Martin-Broto	Javier	Medical Oncology	Spain
Mechtersheimer	Gunhild	Pathology	Germany
Messiou	Christina	Radiology	UK
Miah	Aisha	Radiation Oncology	UK
Pink	Daniel	Medical Oncology	Germany
Reichardt	Peter	Medical Oncology	Germany
Romagosa	Cleo	Pathology	Spain
Rothermundt	Christian	Medical Oncology	Switzerland
Rutkowski	Piotr	Surgery	Poland
Safwat	Akmel	Radiation Oncology	Denmark
Sangalli	Claudia	Radiation Oncology	Italy
Szkandera	Joanna	Medical Oncology	Austria
Thway	Khin	Pathology	UK
Tunn	Per-Ulf	Surgery	Germany
Van der Graaf	Winette	Medical Oncology	The Netherlands
Van Houdt	Winan	Surgery	The Netherlands
Wardelmann	Eva	Pathology	Germany
Zachariah	Ralph	Medical Oncology	Switzerland
Advisors			
Botter	Sander	Patient Advocat	Switzerland
Cerny	Thomas	Medical Oncology	Switzerland

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